DRUG INTERACTIONS

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The term *drug interaction* is applied most frequently to those situations in which the actions of one drug are altered by the concurrent use of another (drug–drug interactions), and to those situations in which the actions of nutrients affect drugs or vice versa (drug–nutrient–food interactions). The concept of drug interaction has also been extended to include situations in which a drug causes alterations of laboratory test results (drug–laboratory test interactions) and in which a drug causes undesired effects in patients with certain disease states (drug–disease interactions).

CONSEQUENCES OF DRUG INTERACTIONS

One of the most important consequences of a drug interaction is an excessive response to one or more of the agents being used. For example, a significantly enhanced effect of agents such as digoxin (e.g., Lanoxin) and warfarin (e.g., Coumadin) can result in serious complications, and the hazards of using agents having central nervous system depressant properties in combination are also well known. Not as well recognized but also very important are those interactions in which drug activity is decreased, resulting in a loss of efficacy. These interactions are especially difficult to detect because they may be mistaken for therapeutic failure or worsening of the disease.

Although some drug interactions develop unexpectedly and are impossible to predict, others are related to known pharmacodynamic and pharmacokinetic properties of the drugs and can be anticipated. However, in considering the number and diversity of the pharmacological actions of each of the agents utilized in many multiple-drug regimens, it is very difficult to predict the magnitude of a specific action of any given drug. These circumstances point to a need not only for maintenance of complete and current medication records for patients, but also for closer monitoring and supervision of drug therapy so that problems can be prevented or detected at an early stage.

The concerns over drug interactions and the advocacy for appropriate precautionary measures are justifiably based on the rapidly growing number of observations and studies in which these problems have been described. However, it is also very important to keep in perspective the potential for the occurrence of an interaction. Caution is needed in evaluating and using the available information to avoid overreacting to a potential problem. Although therapeutic alternatives might be considered and/or steps taken to more closely monitor combination therapy, patients must not be deprived of therapy from which they can benefit. The appropriate clinical perspective must be exercised if optimal therapy is to be achieved.

Sometimes a second drug is prescribed intentionally to modify the effects of the first. Such an approach might be used in an effort to enhance the effectiveness or to reduce the adverse effects of the primary agent. In these situations, the efficacy and/or safety of a drug is increased, which indicates that drug interactions are not always harmful but also can be beneficial.

FACTORS CONTRIBUTING TO THE OCCURRENCE OF DRUG INTERACTIONS

A number of factors contribute to the occurrence of drug interactions; the most important factors will be discussed.

Multiple Pharmacological Effects

Most drugs used in current therapy exhibit more than one type of pharmacological action and have the capacity to influence many physiological systems. Therefore, two concomitantly administered drugs will often affect some of the same systems. When considering the potential for interactions between drugs, there is often a tendency to focus on the primary effects of the drugs involved and to overlook their secondary actions. As an example, combined therapy with a phenothiazine antipsychotic [e.g., chlorpromazine (Thorazine)], a tricyclic antidepressant [e.g., amitriptyline (e.g., Elavil)], and an antiparkinsonian agent [e.g., trihexyphenidyl (e.g., Artane)] is employed in some patients. Each of these agents has a considerably different primary effect; however, all three possess anticholinergic activity. Even though the

anticholinergic effect of any one of the drugs may be slight, the additive effects of the three agents may be significant.

Multiple Prescribers

Some individuals go to more than one physician, and it is common for a patient to be treated by one or more specialists in addition to a family physician. Some patients are also seeing other health professionals (e.g., dentists, podiatrists, etc.), who may prescribe medication. It is frequently difficult for one prescriber to become aware of all the medications that have been prescribed by others for a particular patient, and many difficulties arise from such situations. For example, one physician may prescribe an antihistamine having sedative properties for a patient for whom another physician has prescribed an antianxiety agent, with the possible consequence of an excessive depressant effect. Even though the patient is seeing different prescribers, he will often have the prescriptions dispensed at the same pharmacy. Therefore, the pharmacist, by maintaining patient medication records, plays an important role in the detection and prevention of drug-related problems.

Concurrent Use of Nonprescription Drugs

Many reports of drug interactions involve the concurrent use of a prescription drug with a nonprescription drug (e.g., aspirin, antihistamines, antacids, etc.). When a physician questions a patient about medications being taken, the patient will often neglect to mention nonprescription medications. Many patients take preparations such as antacids, laxatives, analgesics, and vitamins for such long periods and in such a routine manner that they do not consider them to be drugs. This information may often be missed when questioning patients, and some physicians and pharmacists prefer to utilize a list of symptoms that might ordinarily be treated with nonprescription drugs when obtaining this information from patients.

Interactions may also result from the concurrent use of two or more products available without a prescription. In some situations, two nonprescription products promoted for different purposes contain the same active ingredient(s), which increases the risk of an excessive response to these agents. Diphenhydramine is included in many products for its antihistamine action but also is included for its sedative effect in many nonprescription sleep aids. Patients are often unaware that the products they purchase for different conditions may contain the same active ingredients. This puts users at increased risk for interaction difficulties due to the use of products they assume are safe since they do not require a prescription.

The observations made with respect to potential interactions involving nonprescription products also apply to the use of herbal products, dietary supplements, and other related products that are available without a prescription. Although much is still to be learned about the properties of these products, many appear to have a potential to interact with prescription medications. Therefore, patients should be asked whether they are using such products.

Patient Noncompliance

For a variety of reasons, many patients do not take medication in the manner intended by the prescriber. Some patients have not received adequate instructions from the prescriber and pharmacist as to when and how to take their medication. In other situations, particularly those involving patients who are taking several medications, confusion about the instructions may develop even though the patient understood them initially. It is understandable that older patients, who may be taking five or six medications several times a day at different times, can become confused or forget to take their medication, although these occurrences are by no means unique to this population.

At times, patients are noncompliant when they do not take enough of their medication. In other instances, interactions can occur due to excessive dosing. For example, some patients double their dose of medication after realizing they forgot to take the initial dose. Other patients may assume that if the prescribed one tablet dose provides partial but not complete relief of symptoms, a two-tablet dose will be more effective.

MECHANISMS OF DRUG INTERACTION

Understanding the mechanisms by which drug interactions develop will be valuable in anticipating such situations and dealing with problems that do develop. Although the circumstances surrounding the development of some drug interactions are complex and poorly understood, the mechanisms by which many interactions develop are well documented and relate to the basic processes by which drugs act and are acted on in the body.

These mechanisms are often generally categorized as being either pharmacodynamic or pharmacokinetic. Included among the pharmacodynamic interactions are those in which drugs that have similar (or opposing) pharmacological effects are administered concurrently and

situations in which the sensitivity or responsiveness of the receptors/tissues to one drug is altered by the action of another. In these situations, there is a change in drug effect without a change in drug plasma concentration. Pharmacokinetic interactions are those in which one agent (designated by some as the "precipitant drug") alters the absorption, distribution, metabolism, or excretion (ADME) of a second agent (the "object drug"), with a resultant change in the plasma concentration of the latter agent. Several mechanisms may be involved in the development of certain interactions.

Pharmacodynamic Interactions

Although pharmacokinetic interactions have been studied and publicized to a greater extent, pharmacodynamic interactions are very common and also present challenging clinical problems. Some of the causes of pharmacodynamic interactions will be discussed.

Drugs having opposing pharmacological actions

Interactions resulting from the use of two drugs with opposing effects should be among the easiest to detect. However, opposing pharmacological actions are sometimes caused by the secondary effects of certain drugs, and this and other factors may preclude early identification of such situations.

Diuretics: Thiazides and certain other diuretics may elevate blood glucose concentrations. When the diuretic is prescribed for a diabetic patient being treated with insulin or one of the oral antidiabetic agents, this effect may partially counteract the glucose-lowering action of the antidiabetic drug, necessitating an adjustment in dosage. Similarly, many diuretics may produce a hyperuricemic effect. Therefore, therapy in patients with gout should be closely monitored, as the hyperuricemic action of a diuretic may necessitate an adjustment in dosage of the agent being used in the treatment of gout.

Drugs having similar pharmacological actions

The most common type of pharmacodynamic interaction is an excessive response attributable to the concurrent use of drugs having similar actions. These potential problems warrant particular attention.

Central nervous system (CNS) depressants: An excessive CNS depressant effect, resulting from the concurrent use of two or more drugs exhibiting a depressant action, represents one of the most dangerous drug related problems. Older patients are especially susceptible to this type of response, and patients experiencing effects such as fatigue and dizziness are at increased risk of falls and injuries, such as hip fractures. Patients also must be advised of the risks of operating motor vehicles or machinery. In considering multiple drug regimens, the prescriber needs to recognize the large number of agents (e.g., antianxiety agents, hypnotics, antipsychotics, tricyclic antidepressants, certain analgesics, and most antihistamines) that can exhibit a depressant effect. Consideration should be given to whether it is necessary to use all the drugs concurrently, and the dosages of the drugs having a depressant effect should be appropriately reduced.

Alcohol and other CNS depressants: The increased CNS depressant effect experienced by most individuals being treated with depressant drugs when they consume alcoholic beverages is among the best known interactions. However, this interaction also illustrates the difficulties in predicting the magnitude of the response experienced by a particular patient, as the response will depend on many variables, including the patient's tolerance of alcohol. Every patient should be alerted to the fact that the depressant effect of the drug prescribed may be enhanced by alcohol. Patients who will not completely avoid alcoholic beverages should be urged to use them only in moderation, particularly when therapy is initiated, and cautioned to observe their own tolerance when such combinations are employed. However, it should be remembered that even though many individuals can take depressant drugs and consume relatively large amounts of alcoholic beverages with no apparent difficulty, this combination can be lethal to some and cause injury to others. Thus, all patients prescribed these drugs need to be warned of the potential interactions.

Drugs having anticholinergic activity: As noted earlier, drugs that differ considerably in their primary pharmacological actions may exhibit the same secondary effects. Some patients treated with antipsychotic agents, such as chlorpromazine, are also given antiparkinsonian agents, such as trihexyphenidyl, to control the extrapyramidal effects of the former. In addition, a number of patients experience depressive symptoms, and a tricyclic antidepressant, such as amitriptyline, might be added to the therapy. These three agents all possess anticholinergic activity, and the additive effect could result in side effects such as dryness of the mouth, blurred vision, urinary retention, constipation, and elevation of intraocular pressure.

While some health professionals might consider side effects such as dryness of the mouth to be minor, these side effects may be especially troublesome in certain patients. For example, persistent dryness of the mouth could make the use of dentures more difficult and cause other dental complications. Increased difficulty in chewing and swallowing may contribute to the problem of malnutrition in some older individuals.

Dryness of the mouth may also result in other problems. For example, the tricyclic antidepressant imipramine (e.g., Tofranil) can cause persistent dryness of the mouth. If nitroglycerin tablets are administered sublingually for the management of exertional angina, the relief of the symptoms may be delayed due to the slower dissolution of the sublingual tablets.

An excessive anticholinergic effect can cause an atropine-like delirium, particularly in older patients. This effect could be misinterpreted as an increase in psychiatric symptoms that might be treated by increasing the dosage of the therapeutic agents that are responsible for the problem. This example points out the difficulty that often exists in distinguishing between the symptoms of the condition(s) being treated and the effects of the drug(s) being employed as therapy. Other potential problems associated with the use of drugs having anticholinergic activity include memory impairment and impairment in self-care capacity.

There have been reports of patients who take a phenothiazine and antiparkinsonian agent concurrently developing severe hyperpyrexia after being exposed to high environmental temperatures and humidity. These combinations may interfere with the thermoregulatory system of the body, and physicians treating patients in hot and humid climates should minimize the outdoor exposure of patients receiving high doses of these agents.

Drugs exhibiting hypotensive effects: Certain antihypertensive drugs, as well as some other classes of medications (e.g., tricyclic antidepressants), can cause orthostatic hypotension, which results in dizziness, lightheadedness, and in more severe cases, syncope. Older patients are more susceptible to this type of response and the associated risks, such as falls and injuries. Appropriate precautions should be exercised whether these agents are given alone or in combination.

Nonsteroidal antiinflammatory drugs (NSAIDs): In some cases, a patient may unknowingly be taking several different products that contain the same NSAID. An arthritic patient whose condition has been managed with ibuprofen obtained via prescription (often at dosage levels at or near the recommended maximum) may purchase a nonprescription ibuprofen product for pain/discomfort not associated with the arthritis. The patient may not know that the two products contain the same drug and that there is an increased risk of adverse effects.

Alteration of electrolyte concentrations

Several important drug interactions occur as a result of therapeutic agents altering the concentrations of electrolytes, such as potassium and sodium. When these drugs are included in a therapeutic regimen, it is important that electrolyte concentrations be periodically monitored.

Digoxin and diuretics: One of the problems associated with the use of most of the commonly employed diuretics [e.g., the thiazides furosemide (e.g., Lasix)], is excessive loss of potassium. Particular caution is necessary in patients also being treated with digoxin, many of whom are also candidates for diuretic therapy. If potassium depletion remains uncorrected, the heart may become more sensitive to the effects of digoxin and arrhythmia may result.

Although potassium supplementation is necessary in some individuals being treated with a potassium-depleting diuretic, the initiation of therapy with such a diuretic must not be viewed as a mandate to provide potassium supplementation. This decision should be based on a consideration of the individual patient's situation and the appropriate parameters should be periodically monitored. It must be recognized that dangers exist if hyperkalemia occurs as a result of excessive supplementation. Although the kidneys are usually able to excrete excessive amounts of potassium rapidly, hyperkalemia may develop, especially in patients with diminished renal function.

In addition to the diuretics, other agents can cause potassium depletion. Prolonged therapy with cathartics and corticosteroids can cause potassium depletion, although this is not likely to occur as quickly or to the same extent as with diuretics.

Lithium and diuretics: Sodium depletion is known to increase lithium toxicity, and it is generally recommended that lithium not be used in patients on diuretic therapy or on a sodium-restricted diet. Even protracted sweating or diarrhea can cause sufficient depletion of sodium to result in decreased lithium tolerance. The sodium depletion caused by diuretics reduces the renal clearance and increases the activity of lithium. However, if preferable therapeutic alternatives are not available, concurrent therapy need not be contraindicated as long as the interaction is recognized and appropriate steps are taken to monitor therapy and adjust the dosage.

Interactions at receptor sites

Examples of interactions occurring at receptor sites include problems involving the use of the monoamine oxidase (MAO) inhibitors [isocarboxazid (Marplan), phenelzine (Nardil), tranylcypromine (Parnate), and procarbazine (Matulane)].

MAO inhibitors and sympathomimetic agents: MAO breaks down catecholamines, such as norepinephrine. When this enzyme is inhibited, the concentrations of norepinephrine within adrenergic neurons increase and drugs that stimulate its release can bring

about an exaggerated response. Interactions between MAO inhibitors and indirectly acting sympathomimetic amines (e.g., amphetamine) develop by this mechanism. If amphetamine is administered to a patient whose stores of norepinephrine have been increased by MAO inhibition, the patient may experience severe headache, hypertension (possibly a hypertensive crisis), and cardiac arrhythmias. The serious consequences associated with these interactions contraindicate the use of these agents in combination.

Most sympathomimetic amines, such as amphetamine, are available only by prescription; others such as phenylephrine and pseudoephedrine, which also are reported to interact similarly with MAO inhibitors, are found in most popular nonprescription cold and allergy preparations. It is important that patients being treated with MAO inhibitors avoid using products containing these agents.

MAO inhibitors and other antidepressants: Product literature and case reports caution against concurrent use of MAO inhibitors with tricyclic antidepressants (e.g., amitriptyline, imipramine) because severe atropine-like reactions, tremors, convulsions, hypothermia, and vascular collapse can occur. The labeling for most of these products warns that therapy with a MAO inhibitor or a tricyclic antidepressant should not be initiated until at least 7–14 days after therapy with the other drug has been discontinued.

Although the labeling for most MAO inhibitors and tricyclic antidepressants warns that concurrent use is contraindicated, there is disagreement as to the degree of risk involved. Several studies show little evidence of interaction. The impression that serious interactions are uncommon, coupled with reports of favorable results with such combinations in selected patients who did not respond to either agent given alone, have led some to conclude that these combinations can be cautiously employed. In patients who are refractory to single antidepressants and who are not candidates for other therapeutic approaches, the potential benefits of combination therapy may outweigh the risks. However, such therapy should be undertaken only by those who are thoroughly familiar with the risks involved and under circumstances in which therapy can be closely monitored.

Very little data regarding the combined use of fluoxetine (Prozac) and a MAO inhibitor are available. It is advised that their combined use be avoided and that at least 14 days elapse between discontinuation of a MAO inhibitor and initiation of treatment with fluoxetine. There are reports of deaths in patients in whom therapy with a MAO inhibitor was initiated shortly after discontinuation of fluoxetine. Due to the long half-lives of fluoxetine and its active metabolite, it is recommended that at least 5 weeks elapse between discontinuation of fluoxetine and initiation of therapy with a MAO inhibitor.

Pharmacokinetic Interactions

Alteration of gastrointestinal absorption

The interactions that involve a change in the absorption of a drug from the gastrointestinal (GI) tract may develop through different mechanisms and be of varying clinical importance. In some situations, the overall absorption of the drug might be reduced and its therapeutic activity compromised. In other circumstances, absorption may be delayed but the same amount of drug is eventually absorbed. A delay in drug absorption is undesirable when a rapid effect is needed to relieve acute symptoms such as pain. However, in other situations, a delay in drug absorption will not be clinically significant, and this is usually the case when a drug is being used on a chronic basis and therapeutic concentrations in the body have already been achieved. As a general guideline, those drugs not completely absorbed under normal circumstances are most susceptible to alterations of GI absorption.

Ketoconazole and antacids: An acidic medium is required to achieve adequate dissolution of ketoconazole (e.g., Nizoral) following oral administration. Therefore, an antacid, histamine H_2-receptor antagonist [e.g., cimetidine (e.g., Tagamet), ranitidine (e.g., Zantac)], or a proton pump inhibitor [e.g., lansoprazole (Prevacid), omeprazole (Prilosec)] is likely to reduce the dissolution, absorption, and effectiveness of the antifungal agent. An antacid should be administered at least 2 h after ketoconazole. The concurrent use of ketoconazole and a histamine H_2-receptor antagonist or proton pump inhibitor is best avoided, and other agents having a lesser potential for interaction should be considered.

Tetracyclines and metals: Tetracyclines can combine with metal ions, such as calcium, magnesium, aluminum, and iron, in the GI tract to form complexes that are poorly absorbed. Thus, the simultaneous administration of certain drugs (e.g., antacids, iron preparations, products containing calcium salts) by patients on tetracycline therapy could result in a significant decrease in the amount of antibiotic absorbed. When two drugs are recognized as having a potential to interact, there is sometimes a tendency to believe that one of them should be discontinued. In the case of the tetracycline–antacid interactions, problems can be avoided by allowing an interval of at least 1 h to separate the administration of the two drugs.

Fluoroquinolones and metals: Aluminum- and magnesium-containing antacids, as well as other products that contain metals (e.g., iron), markedly reduce the absorption and serum concentrations of the fluoroquinolone derivatives [e.g., ciprofloxacin (Cipro)], probably as a result of the metal ions complexing with the antiinfective agent. Antacids or other metal-containing products must not be administered at the same time as a fluoroquinolone, and the labeling for most of the fluoroquinolones designates a minimum interval of time that should separate the administration of the two drugs. For example, it is recommended that moxifloxacin (Avelox) be taken at least 4 h before or 8 h after taking antacids or other metal-containing products.

Cholestyramine and colestipol: Other interactions involving complexation might be anticipated when cholestyramine (e.g., Questran) and colestipol (Colestid) are used. These resinous materials, which are not absorbed from the GI tract, bind with bile acids and prevent their reabsorption. In addition, cholestyramine and colestipol can bind with drugs (e.g., digoxin and warfarin) that are present in the GI tract. To minimize the possibility of an interaction, the interval between the administration of cholestyramine or colestipol and another drug should be as long as possible.

An interesting application of this interaction is seen with the use of leflunomide (Arava) in the treatment of rheumatoid arthritis. Leflunomide can cause fetal harm if administered during pregnancy, and it has an active metabolite that can persist in the system for at least 2 years. If a woman of childbearing potential discontinues use of leflunomide, it is recommended that cholestyramine (8 g 3 times a day for 11 days) be used to accelerate the elimination of the drug and its active metabolite.

Food: Food can influence the absorption and activity of a number of drugs. In some situations, absorption is delayed but not reduced, whereas in other circumstances, the total amount of drug absorbed is reduced. The effect of food in influencing drug absorption is often due to slower gastric emptying. However, food may also affect absorption by binding with drugs, by decreasing the dissolution rate of solid dosage forms, or by altering the pH of the GI contents.

The presence of food in the GI tract reduces the absorption of many antiinfective agents. Although there are some exceptions (e.g., penicillin V, amoxicillin, and doxycycline), it is generally recommended that penicillin and tetracycline derivatives, as well as certain other antiinfective agents, be given at least 1 h before meals or 2 h after meals to achieve optimum absorption.

Alendronate and food: Food and some beverages (e.g., orange juice, coffee, and mineral water) may markedly reduce the bioavailability of alendronate (Fosamax). Therefore, the drug should be administered at least 30 min before the first food, beverage, or medication of the day, with plain water only.

Acarbose or miglitol and food: Some medications should be administered with food for optimum benefit. Acarbose (Precose) and miglitol (Glyset) are effective in the treatment of diabetes mellitus because they delay the digestion of ingested carbohydrates and reduce the elevation of blood glucose concentrations following meals. Maximum effectiveness is attained when doses are administered at the start (with the first bite) of each main meal.

MAO inhibitors and tyramine: There have been reports of serious reactions (e.g., hypertensive crises) occurring in patients being treated with a MAO inhibitor following ingestion of foods with a high content of pressor substances, such as tyramine.

Tyramine is metabolized by MAO, and normally these enzymes in the intestinal wall and in the liver protect against the pressor actions of amines in foods. However, when these enzymes are inhibited, large quantities of unmetabolized tyramine can accumulate and act to release norepinephrine from adrenergic neurons where greater-than-usual stores of this catecholamine are concentrated as a result of MAO inhibition. Among the foods having the highest tyramine content are aged cheeses (such as cheddar), certain alcoholic beverages (e.g., Chianti), pickled fish (e.g., herring), concentrated yeast extracts, and broad-bean pods (also known as fava beans or Italian green beans).

The pharmaceutical companies that market the MAO inhibitors have developed lists of dietary items to avoid when taking taking one of these agents. This information should be provided to and discussed with each patient who is prescribed a MAO inhibitor.

Grapefruit juice: Grapefruit juice is reported to increase the serum concentrations and activity of a number of medications, such as certain calcium channel blocking agents [e.g., felodipine (Plendil) and nisoldipine (Sular)], certain HMG–CoA reductase inhibitors [e.g., lovastatin (Mevacor)], and cyclosporine (e.g., Neoral). The bioavailability of most of these agents is generally low, primarily as a result of extensive first-pass metabolism. Components of grapefruit juice possibly reduce the activity of the cytochrome P450 enzymes (primarily CYP3A4) in the gut wall, which are involved in the metabolism of these agents. As a result, larger amounts of unmetabolized drug are absorbed and serum concentrations are increased.

Alteration of distribution

Interactions involving an alteration of distribution may occur when two drugs that are capable of binding to proteins are administered concurrently and one agent displaces the other. Most significant are the situations in which two drugs are capable of binding to the same sites on the protein (competitive displacement). Since protein-binding sites are limited in number, the drug that has the greater affinity for the binding sites will displace the other from plasma or tissue proteins. The protein-bound fraction of a drug in the body is not pharmacologically active. However, an equilibrium exists between bound and unbound fractions, and as the unbound or "free" form of the drug is metabolized and excreted, the bound drug is gradually released to maintain the equilibrium and pharmacological response.

The risk of an interaction occurring is greatest with those drugs that are highly protein bound (more than 90%) and that also have a small apparent volume of distribution. Since only a small fraction of the drug would ordinarily be available in the free form, the displacement of even a small percentage of the amount that is bound to proteins could produce a considerable increase in activity.

Methotrexate: Methotrexate is highly bound to plasma proteins, and agents such as the salicylates may be capable of displacing it from binding sites. Salicylates may also increase the action of methotrexate by inhibiting its renal excretion. The potential for toxicity with methotrexate dictates caution in all situations in which it is used.

Stimulation of metabolism

Drug metabolism occurs primarily in the liver and most commonly involves oxidation, reduction, hydrolysis, and conjugation reactions. Quantitatively, the most important hepatic enzymes are the cytochrome P450 enzymes that have been divided into families and subfamilies (e.g., CYP3A4) based on the similarity of their amino acid sequences. These enzymes are responsible for the metabolism of a large number of drugs.

Many drug interactions result from an effect frequently referred to as enzyme induction: the ability of one drug to stimulate the metabolism of another, most often by increasing the activity of liver enzymes. Enzyme induction usually results in increased metabolism and excretion, and reduces the effect of the agent that is metabolized by the hepatic enzymes. Phenobarbital (and other barbiturates), phenytoin, carbamazepine (e.g., Tegretol), and rifampin (e.g., Rifadin) are among the agents best recognized as causing enzyme induction.

Warfarin and phenobarbital: Phenobarbital, by causing enzyme induction, can increase the rate of metabolism of warfarin. The result of this interaction is a decreased response to the anticoagulant and an increased risk of thrombus formation if the interaction is not recognized.

Smoking: The polycyclic hydrocarbons in cigarette smoke may increase the activity of oxidative enzymes, with the result that certain therapeutic agents [e.g., diazepam (e.g., Valium), propoxyphene (Darvon), theophylline, chlorpromazine, and amitriptyline] are metabolized more rapidly and their effect is decreased. In addition to monitoring therapy carefully with drugs that are metabolized by hepatic enzyme systems in patients who are moderate or heavy smokers, caution must also be exercised if a patient treated with such a medication discontinues smoking. For example, if therapy with a tricyclic antidepressant is initiated in a patient who is a heavy smoker, the maintenance dosage will be determined during the time period in which the enzyme-inducing action of smoking is decreasing the effect of the medication. If the patient stops smoking and is still taking the medication, the dosage that had been appropriate is now likely to be excessive and will have to be reduced.

Inhibition of metabolism

There are numerous situations in which one drug inhibits the metabolism of a second agent, usually resulting in a prolonged and intensified activity of the latter.

Mercaptopurine or azathioprine and allopurinol: Allopurinol (e.g., Zyloprim), by inhibiting the enzyme xanthine oxidase, reduces the production of uric acid, which is the basis for its use in the treatment of gout. Xanthine oxidase also has an important role in the metabolism of such potentially toxic drugs as mercaptopurine (e.g., Purinethol) and azathioprine (e.g., Imuran). When xanthine oxidase is inhibited by allopurinol, the effect of these agents can be markedly increased. When allopurinol is given in doses of 300—600 mg/day concurrently with either of these drugs, it is advised that the dose of mercaptopurine or azathioprine be reduced to about one-third to one-fourth the usual dose.

Cimetidine: Since cimetidine may inhibit certain metabolic pathways, an increased action of concurrently administered drugs that are metabolized via these pathways should be anticipated. For example, cimetidine may inhibit the metabolism of diazepam and certain other benzodiazepines, and the sedative effect of these agents may be enhanced as a result of the interaction. Particular caution is necessary in older patients who may exhibit an increased sensitivity to the depressant effects of the

benzodiazepines, even when one of these agents is given alone.

The metabolism of lorazepam (e.g., Ativan), oxazepam (e.g., Serax), and temazepam (e.g., Restoril) are not likely to be affected, and one of these agents may be preferred when a benzodiazepine is indicated in a patient being treated with cimetidine. The experience with ranitidine (e.g., Zantac), famotidine (Pepcid), and nizatidine (Axid) suggests that these agents are not likely to inhibit hepatic enzyme systems, and these other histamine H_2-receptor antagonists are less likely than cimetidine to interact with other drugs that are metabolized via these pathways.

Macrolide antibiotics: Erythromycin may significantly increase serum concentrations of medications such as theophylline by inhibiting their hepatic metabolism. Clarithromycin (Biaxin) and troleandomycin appear to interact with other medications in a manner similar to erythromycin, whereas azithromycin (Zithromax) is unlikely to interact with these agents.

Fluoroquinolones: Ciprofloxacin and enoxacin (Penetrex) may markedly increase serum concentrations of medications such as theophylline by inhibiting their hepatic metabolism. Certain other fluoroquinolones, such as levofloxacin (Levaquin), are not likely to inhibit hepatic enzyme systems and interact with these medications.

Alteration of excretion

Many drugs and their metabolites are excreted via the kidneys. The most important clinical implications of altering renal excretion involve the use of drugs that are excreted in their unchanged form or in the form of an active metabolite. Thus, substances with pharmacological activity are being reabsorbed or excreted to a greater extent when renal excretion is altered.

Salicylates: A change in urinary pH will influence the ionization of weak acids such as salicylates as well as weak bases (e.g., amphetamine), thereby affecting the extent to which these agents are reabsorbed and excreted. When a drug is in its nonionized form, it will more readily diffuse from the urine back into the blood. Therefore, an acidic drug will have a larger proportion of the nonionized drug in an acid urine than in an alkaline urine, where it will primarily exist as an ionized salt. The result is that acidification of the urine may result in increased salicylate concentrations and a prolonged and perhaps intensified drug action. The risk of a significant interaction is greatest in patients who take large doses of salicylates (e.g., for arthritis).

Penicillins and probenecid: A number of organic acids are actively transported from the blood into the tubular urine and vice versa. In some situations, these agents interfere with each other's excretion. Probenecid (e.g., Benemid) can increase the serum concentrations and increase and prolong the activity of penicillin derivatives by blocking their tubular secretion. This is an interaction that has been used to therapeutic advantage in the treatment of certain infections.

Methotrexate and NSAIDs: NSAIDs are reported to increase the activity and toxicity of methotrexate, presumably by inhibiting its active renal tubular secretion. Other mechanisms probably also contribute to an increase in serum methotrexate concentrations. Most of the patients in whom these interactions were reported were receiving high-dose methotrexate therapy for neoplastic disorders. However, caution should also be exercised in patients receiving lower doses.

Digoxin and quinidine: Studies have noted significantly greater serum digoxin concentrations when quinidine was administered concurrently than when digoxin was given alone. Digoxin is actively secreted in the renal tubules, and a primary cause of the quinidine-induced increase in serum digoxin concentrations appears to be a reduction in the renal clearance of digoxin. However, quinidine may also reduce the nonrenal clearance of digoxin.

Although other mechanisms may be involved in the development of drug interactions, the ones cited are the most important. More than one mechanism may be responsible for certain interactions and these mechanisms may work in concert or in opposition to determine the resulting effect. Still other drug interactions develop by mechanisms yet to be identified.

Significant limitations often exist in trying to predict the results of combination therapy. In the following discussion, guidelines are provided to reduce the risk of the occurrence of drug interactions.

REDUCING THE RISK OF DRUG INTERACTIONS

Reducing the risk of drug interactions is a challenge that embraces a number of considerations. The following are guidelines to reduce and manage drug interactions.

1. Identify patient risk factors: Factors such as age, the nature of the patient's medical problem (e.g., impaired renal function), dietary habits, smoking, and problems such as alcoholism influence the effect of certain drugs and should be considered during the initial patient interview.
2. Take a thorough drug history and maintain complete patient medication records: An accurate and complete record of both the prescription and nonprescription medications a patient is taking must be obtained prior

to changing the therapeutic regimen. Numerous interactions have resulted from a lack of awareness of medications prescribed by another physician, or of nonprescription medications the patient did not consider important enough to mention. By maintaining patient medication records, the pharmacist is in an excellent position to detect potential problems and initiate the necessary steps to minimize or avoid them.

3. Be knowledgeable about the actions of the drugs being utilized: The knowledge of the properties and the primary and secondary pharmacological actions of each of the agents used, or being considered for use, is essential if the interaction potential is to be accurately assessed.
4. Consider therapeutic alternatives: In most cases, two drugs that are known to interact can be administered concurrently as long as adequate precautions are taken (e.g., closer monitoring of therapy or dosage adjustments to compensate for the altered response). However, in those situations in which another agent with similar therapeutic properties and a lesser risk of interaction is available, the other agent should be used.
5. Avoid complex therapeutic regimens where possible: The number of medications used should be kept to a minimum. In addition, the use of medications or dosage regimens that permit less frequent administration may help avoid interactions that result from an alteration of absorption (e.g., when a drug is administered in close proximity to meals).
6. Educate the patient: Patients often know little about their illness, let alone the benefits and problems that could result from drug therapy. Individuals who understand this information are more likely to comply with instructions for administering medications and are more attentive to the development of symptoms that could be early indicators of drug-related problems. Patients should be encouraged to ask questions about their therapy and to report any excessive or unexpected responses. There should be no uncertainty on the part of the patient as to how to use medications in the safest, most effective way.
7. Monitor therapy: The risk of drug-related problems warrants close monitoring, not only for the possible occurrence of drug interactions but also for adverse effects occurring with individual agents and noncompliance. Any change in patient behavior should be suspected as drug-related until that possibility is excluded.
8. Individualize therapy: Although the development of a therapeutic regimen that meets the specific needs of individual patients is inherent in many of the above guidelines, the importance of this consideration cannot be too strongly emphasized. Wide variations in the response of patients to the same dose of certain drugs are well recognized. It is difficult to predict the response to many therapeutic agents when they are given alone; the challenge and limitations in anticipating the response to a multiple drug regimen are even greater. Therefore, priority should be assigned to the needs and clinical response of the individual patient, rather than to the usual dosage recommendations, standard treatment, and monitoring guidelines.
9. Involve the patient as a partner in health care. The best efforts of the health professionals involved in the patient's care will fall short of the desired goals unless the patient and/or the family participates in, understands, and complies with decisions regarding the therapeutic regimen. If the optimal benefits of therapy are to be achieved with minimal risk, each participant must be knowledgeable about and diligent in fulfilling his responsibilities.

The following publications are recommended as comprehensive references in which detailed information regarding specific interactions is provided:

BIBLIOGRAPHY

Hansten, P.D.; Horn, J.R. *Drug Interactions Analysis and Management*; Facts and Comparisons: St. Louis, 2001.

Tatro, D.S. *Drug Interaction Facts*; Facts and Comparisons: St. Louis, 2001.